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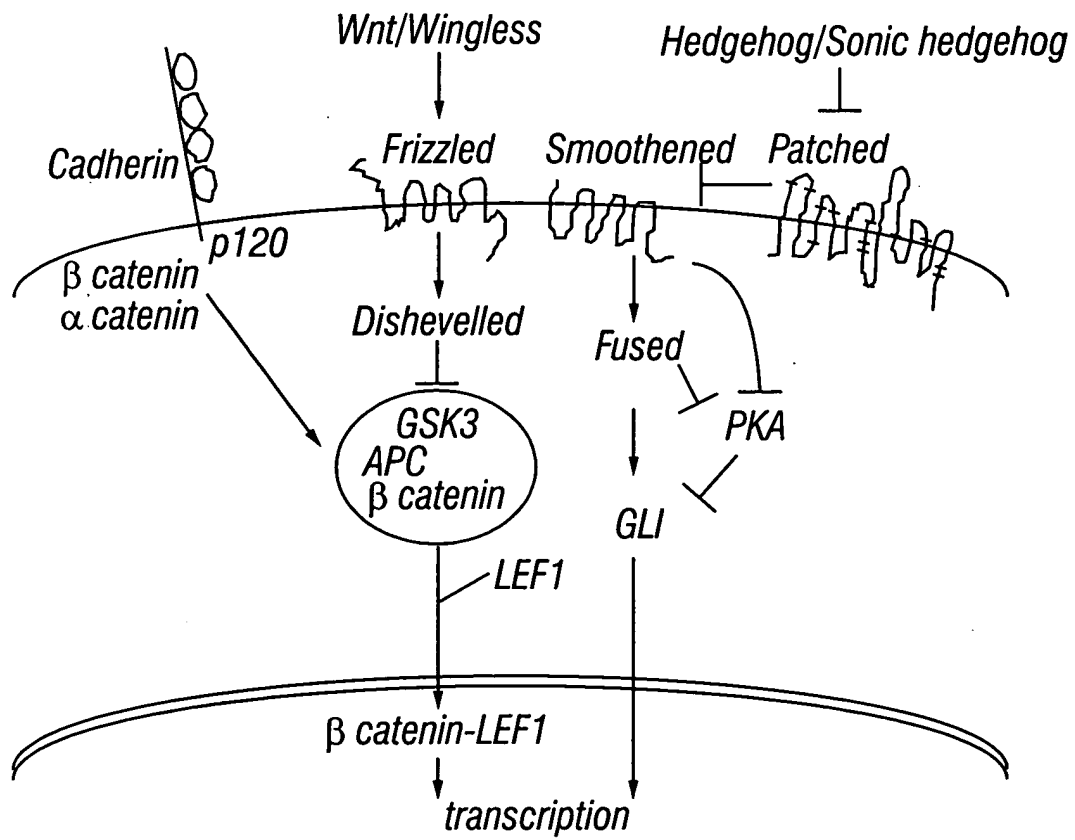


FIG. 1

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Alignment of several frizzled family members

→ amino terminal domain

fz3/mouse -----MAVSWIVFDLWLLTVFLG---QIGGHS-----LFSCE.
fz4/mouse -----MAWPGTGPS---SRGAPGGVGLRLGLLLQFLLLRPTLGFGD-----EEERRCD
fz8/mouse -----MEWGYL-----LEVTSLLAALAVLQRSSG-AAAASAK-----ELACQ
fz5/human -----MARPD-----SAPPSLL--LLLLAQLVG-RAAAASK-----APVCQ
fzd9/human -----MAVAPLRGALLWQLLAAGGALEIGRFD-----PERGRG-----AAPCQ
fzl/rat LEAPLLLGVRAQPAG---QVSG-PGQQRPPPPQPPQGG--QQYNGERG--ISIPDHGYCQ
fz2/rat -----MRARSAL---PRSALPRLLLPLLLPAAGP--AQFHGEKG--ISIPDHGFCQ
fz/Dros ILPTLIQGVQRYDQS---PLDASPYRSGGGLMASSG---TELDG-----LPHHNRCE
fz2/Dros/ GLVLLLTSCRADGPL-----HSADHGMGGMGMGGHGLD-ASPAPGYGVPAPKDPNLRCE

*:

CRD

fz3/mouse PITLRMCQDLPYNTTFMPNLLNHYDQQTAAALAMEPFHPMVNLDCSRDFRPFCLCALYAPIC
fz4/mouse PIRIAMCQNLGYNVTKMPNLVGHELOTDALQLTTFTPLIQYGCSSQLQFFLCSSVYVPMC
fz8/mouse EITVPLCKGIGYNYTYMPNQFNHDTQDEAGLEVHQFWPLVEIQCSDDLKFFLCSSMYTPIC
fz5/human EITVPMCRGIGYNLTHMPNQFNHDTQDEAGLEVHQFWPLVEIQCSDDLRFLLCTMYTPIC
fzd9/human AVEIPMCRGIGYNLTRMPNLLGHTSQGEAAELAEFAPLVQYGCCHSLRFFLCSSLYAPMC
fzl/rat PISIPCLTDIAYNQTIMPNLLGHTNQEDAGLEVHQFYPLVKVQCSAELKFFLCSSMYAPVC
fz2/rat PISIPCLTDIAYNQTIMPNLLGHTNQEDAGLEVHQFYPLVKVQCSPELRFLLCTMYAPVC
fz/Dros PITISICKNIPYNTIMPNLIGHTKQEEAGLEVHQFAPLVKIGCSDDLQFLCSSLVYPVC
fz2/Dros/ EITIPMCRGIGYNMTSFPNEMNHETQDEAGLEVHQFWPLVEIKCSDDLKFFLCSSMYTPIC
: : * .: ** :** . * * * : : *::: * : :*: *:*

CRD

fz3/mouse M-EYGRVTLPCCRQCQRAYSECSKLMEMFG-VPWPEDECSRFPCD-EPYPRIVDLN--
fz4/mouse TEKINIPIGPCGGMCLSVKRRCEPVLREFG-FAWPDTLNCSKFPPQN-DHNHMCMEGP--
fz8/mouse LEDYKKPLPPCRSVCERAKAGCAPLMRQYG-FAWPDRMRCDRLPEQG-NPDTLCMDYN-R
fz5/human LPDYHKPLPPCRSVCERAKAGCSPLMRQYG-FAWPERMSCDRLPVLGRDAEVLCDYN-R
fzd9/human TDQVSTPIACRPMCEQARLRCAPIMEQFN-FGWPDSLDCARLPTRN-DPHALCMEAPEN
fzl/rat T-VLEQALPPCRSLCERA-QGCEALMNKFG-FQWPDTLKCEKFPVHG--AGELCVGQNTS
fz2/rat T-VLEQAIPPCRSICERARQGCEALMNKFG-FQWPERLRCEHFPRHG--AEQICVGQNHHS
fz/Dros T-ILERPIPPCRSLCESA-RVCEKLMKTYN-FNWPENLECSKFVHG--GEDLCVAENTT
fz2/Dros/ LEDYHKPLPVCRSVCERARSGCAPIMQOYS-FEWPERMACEHLPLHG-DPDNLCMEQPSY

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FIG. 2A

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fz3/mouse -----LVGDPT-----
fz4/mouse ---GDEE-----VPLPHKTP-
fz8/mouse TDLTTAAPSPRRLLLLPPPPPPGEQPPSGSGHSRPPGARPPHRGGSSRGSGDAAAAPPSSRG
fz5/human SEATTAPPRP---FPAKP---TLP--G----PP-----G---APAS-GG
fzd9/human ATAGPAEPHK---GLGM---LP-----VAPRPAPPPG
fz1/rat   DKGTPTPSL-----L-----PEFWTSNPQHG
fz2/rat   EDG--TPAL-----L-----TTAPPSGLQPG
fz/Dros   SSA-----STAATPTRSVA
fz2/Dros/ TEAGSGGSSG---GSGG---SGSGSGSGGKRKQGGSGSGGAGGSSGSTSTKPCR-GR
amino terminal domain continued

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                                     TM1
fz3/mouse  YSFLHVRDCSPPCPN-----MYFRREELSFARYFIGLISIICLSATLFTFLTLIDVTR
fz4/mouse  --LNCVLKCGYDAG-----LYSRSAKEFTDIWMAVWASLCFISTTFTVLTLIDSSR
fz8/mouse  -KTGQIANCALPCHN-----PFFSQDERAFTVFWIGLWSVLCFVSTFATVSTFLIDMER
fz5/human  -RTGQVPNCAVPCYQ-----PSFSADERTFATFWIGLWSVLCFISTSTTVATFLIDMDT
fzd9/human --RSCAPRCGPGVEV-----FWSRRDKDFALVWMAVWSALCFFSTAFTVLTLLEPHR
fz1/rat    LG EK---DCGAPCEPTKVYGLMYFGPEELRFSRTWIGIWSVLCCASTLFTVLTYLVDMMR
fz2/rat    LG ER---DCAAPCEPARPDGSMFFSHHHTRFARLWILTWSVLCCASTFTVTTSVLAMQR
fz/Dros    VGGKDLHDGAPCH-----AMFFPERERTVLRVWGSWAACVASCFTVLTLTLIDSSR
fz2/Dros/  QRIAGVPNCGIPCKG-----PFFSNDEKDFAGLWIALWSGLCFCSTLMTLTTFIIDTER
          *                               :  :  *           :  *

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                                     TM2  extracellular domain loop 1
fz3/mouse  FRYPERPIIFYAVCYMMVSLIFFIGFLE-DRVACNASSP-----
fz4/mouse  FSYPERPIIFLSMCYNIYSIAYIVRLTVGRERISCDF-----
fz8/mouse  FKYPERPIIFLSACYLFVSVGYLVRLVAGHEKVACSGGAPGAGGRGGAGGAAAAGAGAAG
fz5/human  FRYPERPIIFLSACYLCVSLGLFLVRLVVGHASVACS-----
fzd9/human FQYPERPIIFLSMCYNVYSLAFLIRAVAGAQSVACD-----
fz1/rat    FSYPERPIIFLSGCTAVAVAYIAGFLE-DRVVCNDKFAE-----
fz2/rat    FRYPERPIIFLSGCTMVSVAYIAGFVLQ-ERVVCNERFSE-----
fz/Dros    FRYPERAIVFLAVCYLVVGACAYVAGLGAG-DSVSCREPPPPVK---LG-----
fz2/Dros/  FKYPERPIVFLSACYFMVAVGYLSRNFLQNEEIACDG-----
* **** : : * . ** . : .

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FIG. 2B

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TM3
fz3/mouse -----AQYKASTVTQGSNKA-CTMLFMVLYFFTMAGSVWVILTITWFLA
fz4/mouse -----EAAEPVLIQEGKNTGCAIFLLMYFFGMASSIWWVILTITWFLA
fz8/mouse RGASSPGARGEYEEELGAVEQHVRVETTPALCTVFLVYFFGMASSIWWVILSLTWFLA
fz5/human R-----EHNHIHYETTPALCTIVFLVYFFGMASSIWWVILSLTWFLA
fzd9/human -----QEAGALYVIQEGLENTGCTLVFLLLYFFGMASLWVVLTLTWFLA
fzl/rat -----DGARTVAQGTKKE-GCTILFMVLYFFSMASSIWWVILSLTWFLA
fz2/rat -----DCYRTVGQGTKKE-GCTILFMVLYFFSMASSIWWVILSLTWFLA
fz/Dros -----RLQMMSTITQGHROTTSCTVLFMALYFCCMAFAWWSCLAFWFLA
fz2/Dros/ -----LLLRESSTGPHSCTLVFLTYFFGMASSIWWVILTFWFLA
: * :: : ... ** ::: :*:

TM4 → extracellular domain loop 2 ←
fz3/mouse AVPKWGSEAIKALLFHASAWGIPGTLTILLAMNKIEGDNISGVCVGLYDVALRYF
fz4/mouse AGLKWGHEAIEMHSSYFHIAAWAIPAVKTIVILIMRLVDADELGLCYVGNQNLDAITGF
fz8/mouse AGMKWGNEAIAQYFHLAALVPSVKSIAVLALSSVDGDPVAGICYVGNQSLDNLRGF
fz5/human AAMKWGNEAIAQYFHLAALVPSVKSITALLSSVDGDPVAGICYVGNQNLNLSLRRF
fzd9/human AGKKWGHEAIEAHGSYFHMAAWGLPALKTIVILTLRKVAGDELGLCYVASTDAAALTGF
fzl/rat AGMKWGHEAIEANSQYFHLAAWAVPAIKTITILALGQVDGDLVSGVCVGLNNVDALRGF
fz2/rat AGMKWGHEAIEANSQYFHLAAWAVPAVKTITILAMQIDGDLVSGVCVGLNRLDPLRGF
fz/Dros AGLKWGHEAIEAKSHLFLVAVAPALQITISVLALAKVEGDILSGVCVFGQLDTHSLGAF
fz2/Dros/ AGLKWGNEAITKHSQYFHLAALVPTVQSVAVLLLSAVDGDPIGICYVGNLNPDLKTF
: **. *: . ** ** * .: * : : .: **: *

TM5
fz3/mouse VLAPLCYVVVGVSLLAGTISLNRVRIEIPLEKE-----NQDKLVKFMIRIGVFSILYL
fz4/mouse VVAPLFTYLVIGTLFIAAGLVALFKIRSNLQK-DG----TKTDKLERLMVKIGVFSVLYT
fz8/mouse VLAPLVIYLFITGTFLLAGFVSLFRIRSVIKQGGP---TKTHKLEKLMIRLGFTVLYT
fz5/human VLGPLVLYLLVGTFLFLLAGFVSLFRIRSVIKQ-GG----TKTDKLEKLMIRIGIFTLLYT
fzd9/human VLVPLSGYLVLGSSFLTGFVALFHIRKIMKT-GG----TNTEKLEKLMVKIGVFSILYT
fzl/rat VLAPLFVYLFITGSFLLAGFVSLFRIRTIMKH-DG----TKTEKLEKLMVRIGVFSVLYT
fz2/rat VLAPLFVYLFITGSFLLAGFVSLFRIRTIMKH-DG----TKTEPLERLMVRIGVFSVLYT
fz/Dros LILPLCIYLSIGALFLLAGFISLFRIRTVMKT-DG----KRTDKLERLMVRIGFFSGLFI
fz2/Dros/ VLAPLFVYLVIGTTFLLAGFVSLFRIRSVIKQGGVGAGVKADKLEKLMIRIGIFSILYT
: * :*: : . :* :: : . : : :*: *

FIG. 2C

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	TM6	extracellular domain loop 3
fz3/mouse	VPLL [→] VVIGCYFYEQAYRGIWETTWIQERCREYHIPCPLYQVTQMS	-----RPDLILFLM [←]
fz4/mouse	VPATCVIACYFYEISNWALFRYSADDS	-----NMAVEML
fz8/mouse	VPA [→] AVVACLFYEQHNRPRWEATHNCPCLRDLQPDQARR	-----PDYAVFML
fz5/human	VPASIVVACLYEQHYRESWEAALTCACPGHDTGQPRAK	-----PEYWVLM
fzd9/human	VPATCVIVCYVYERLNMDFWRLRATEQPCAAAAGPGGRRDCSLP	----GGSVPTVAVFML
fzl/rat	VPATIVIACYFYEQAFRDQWERSWVAQSCSKSYAIPCPHLQGGGVPPHPPMSPDFTVFM	
fz2/rat	VPATIVIACYFYEQAFREHWERSWVSQHCKSLAIPCPAHT	-----PRTSPDFTVYMI
fz/Dros	LPAVGLLGCLFYEYNFDEWMIQWHRDICKPFSIPCPAARAPGS	----PEARPIFQIFMV
fz2/Dros/	VPATIVIGCYLYEAA [→] YFEDWIKALACPCAQVK	--GPGKK-----PLYSVLML
	* : . . *	::
	TM7	
fz3/mouse	KYLMALIVGIPSI [→] FWVGSKKTCFEWASFFHGRRKKEIVNESRQVLQEPDFAQSLLRDPNT	
fz4/mouse	KIFMSLLVGITSGMWIWSAKTLHTWQKCS	-----NRLVNSGKVK-----REKRG
fz8/mouse	KYFMCLVVGITSGVWVWSGKTLESWRALC	-----TRCCWASKGAAGAGAGGSG
fz5/human	KYFMCLVVGITSGVWVWSGKTVESWRRFT	-----SRCCCRPR-----RGHK-
fzd9/human	KIFMSLVVGITSGVWVWSKTFQ [→] TWQSLC	-----YRKIAAGRARA-----KACRA
fzl/rat	KYLMTLIVGITSGFWIWSGKT [→] LNSWRKFY	-----TRLTNSK-----QGETT
fz2/rat	KYLMTLIVGITSGFWIWSGKT [→] LHSWRKFY	-----TRLTNSR-----HGETT
fz/Dros	KYLC [→] SMLVGV [→] TSSVWLYSSKTMVSWRNFV	-----ERLQ [→] GKEPRT-----RAQAY
fz2/Dros/	KYFMALAVGITSGVWVWSGKTLESWRRFW	-----RRLGAPDRTGANQALIKOR
	: : : * : . * : * * *	:

FIG. 2D

Sequence alignment of a portion of the aminoterminal extracellular region of human Frizzled receptors

HF21	VCQNTSDKGT---PSLLPEFWTSNPQHGGGCHRG	-----GFPGGAG---ASERKGFSCPR
HF22	VCQNHSE [→] DGA	----PALLTTAPPPGLQPCAGGTPG-----GPGGGGAPPRYATLEHPFHC
HF23	LVDLNLG	----EPTEGAPV-----AVQRDYG-----FWC
HF24	CMEGPGD	-----EE-----VPLPHKTPI-----QP
HF25	CMDYNRSEATTAPPRPPAKPTLPG	-----PPGA-----PASGG---ECPAGGPFV-----CKC
HF26	TFDPHTEF	----LGPKKTE-----QVQRDIG-----FWC
HF27	VCQNTSDGSGGPGGGPTAYPTAPYLPDLPTALPPG	-----ASDCRGRPAF-----PFSC
HF28	CMDYNRTDLTTAAPSPPRRLP [→] PPPP	---GEQPPSGSGHGRPPGARPPHRRGGGGGGDAAAPPARGGGGGKARPPGGGAAP---CEPGCQC
HF29	CMEAPENA-TAGPAEPHKGLGMLPV	-----APRPARPPG-----DLGP
HF210	NYLCMEAPNN	----GSDEPTRGSGLFPP-----LFRPQRPHSAQ---EHP

FIG. 3

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Effect of FZD on SNU1076 cells

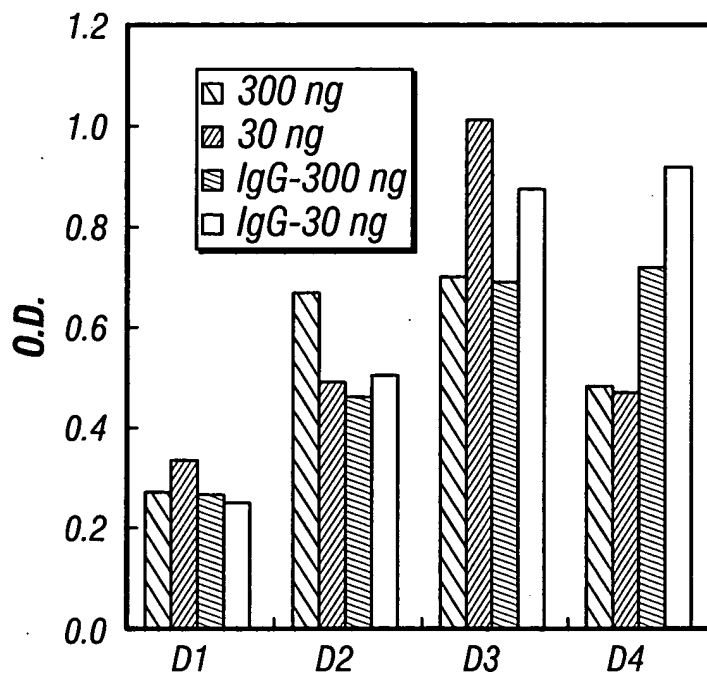


FIG. 4

Effect of antibodies SNU 1076 Cells

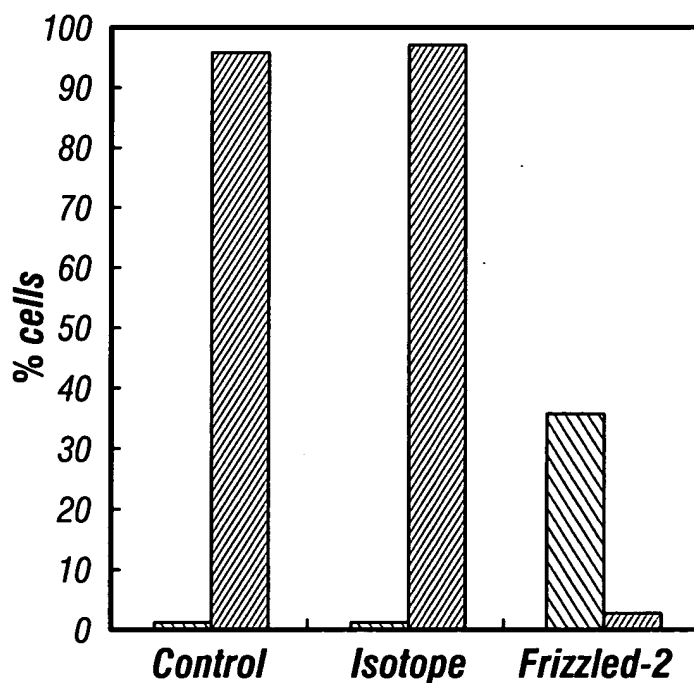


FIG. 5

Graphical Representation of an Olfactory Protein showing Amino-terminal and three Extracellular Domain Loops (from PCT WO 92/17585)

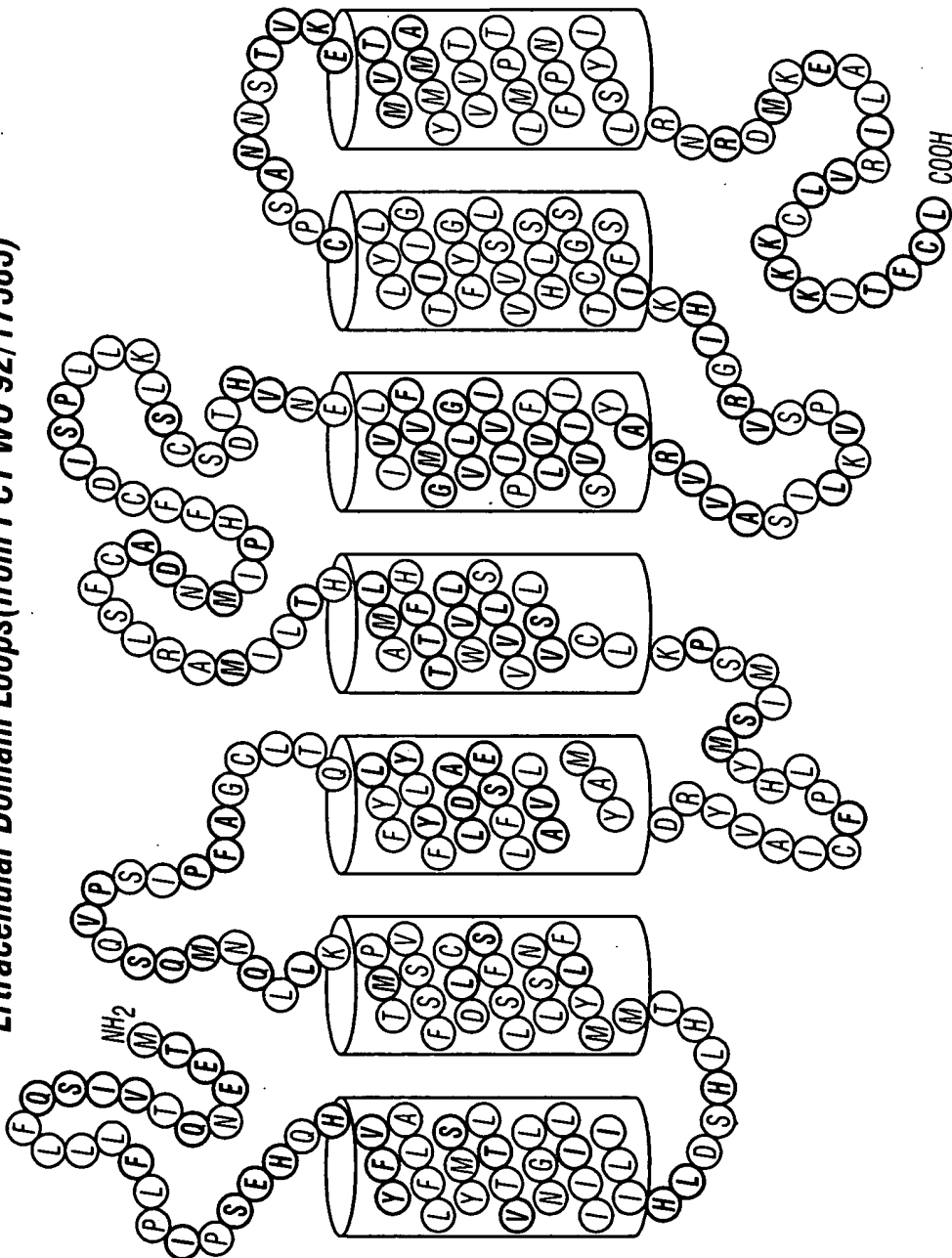


FIG. 7

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Effect of antibodies SNU 1076 Cells

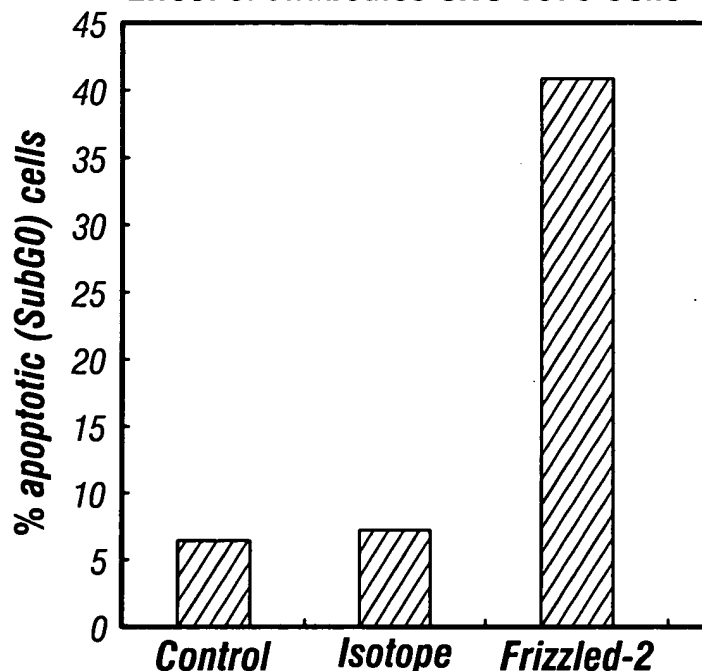


FIG. 6

→ amino terminal domain

HFZ1	MAEEEAPKKSRAAGGASWELCAGALSARLAEEGSGDAGGRRRPPVDPRRLARQLLLLLLW
MFZ1	MAEEAAPSESRAAGR-LSLELCAEALPGRREEVGHEDTASHRRPRADPRRWASGLLLLLLW
HFZ2	-----MRPRSALPRLLLPLL
HFZ3	-----MAMTWIVFSLWPLTV
MFZ3	-----MAVSWIVFDLWLLTV
HFZ4	-----MAWRGAGPSVPGAPGGVGLSLGLLLQ
MFZ4	-----MAWPGTGPPSRGAPGGVGLRLGLLLQ
HFZ5	-----MARPDPSAPPSLL--LLL
HFZ6	-----MEMFTFLLTCI
MFZ6	-----MERSPFLLACI
HFZ7	-----MRDPGAAAPLSSLGLCALVLA
MFZ7	-----MRGPGTAASHSPLGLCALVLA
HFZ8	-----MEWGYLLEVTSLAALAL
MFZ8	-----MEWGYLLEVTSLAALAV
HFZ9	-----MAVAPL-RGALLLWQLLA
MFZ9	-----MAVPPLLRGALLLWQLLA
HFZ10	-----MQRPGPRLWLVLQ

FIG. 8A

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HFZ1	LLEAPLLLGVRAQAAGQPGQPGPGQPPPPPPQQQSQQYNGERGISVPDHGYCQPIS
MFZ1	LLEAPLLLGVRAQAAGQVSG---PGQQA PPPPQ PQQSQQYNGERGISIPDHGYCQPIS
HFZ2	LLPA-----A-----GPAQFHGEKGISIPDHGFCQPIS
HFZ3	FMGHI-----GGHSLFS-----CEPIT
MFZ3	FLGQI-----GGHSLFS-----CEPIT
HFZ4	LLLLLG-----PARGFGDEEE-----RRC DPIR
MFZ4	FLLLLR-----PTLGFGDEEE-----RRC DPIR
HFZ5	LAQLVG-----RAAAASKAPV-----CQEIT
HFZ6	FLPLL-----RGHSLFT-----CEPIT
MFZ6	LLPLV-----RGHSLFT-----CEPIT
HFZ7	LLGAL-----SAGAGAPYHGEKGISVPDHGFCQPIS
MFZ7	LLGAL-----PTDTRAQPYHGEKGISVPDHGFCQPIS
HFZ8	LQRSSG-----AAAASAKELA-----CQEIT
MFZ8	LQRSSG-----AAAASAKELA-----CQEIT
HFZ9	AGGAAL-----EIGRFDPERGR---GAAPCQAVE
MFZ9	TGGAAL-----EIGRFDPERGR---GPAPCQAME
HFZ10	VMGSCA-----AISSMDMERP---GDGKCQPIE

*:

HFZ1	IPLCTDIAYNQTIMPNLLGHTNQEDAGLEVHQFYPLVKVQCSAELKFFLCSMYAPVCT-V
MFZ1	IPLCTDMAYNQTIMPNLLGHTNQEDAGLEVHQFYPLVKVQCSAELKFFLCSMYAPVCT-V
HFZ2	IPLCTDIAYNQTIMPNLLGHTNQEDAGLEVHQFYPLVKVQCSPELRFFLCSMYAPVCT-V
HFZ3	LRMCQDLPYNTTFMPNLLNHYDQQTAAALAMEPFHPMVNLDCSRDFRPFALCALYAPICM-E
MFZ3	LRMCQDLPYNTTFMPNLLNHYDQQTAAALAMEPFHPMVNLDCSRDFRPFALCALYAPICM-E
HFZ4	ISMCQNLGYNVTKMPNLVGHELQTDALQLTTFTPLIQYGCSSQLQFFLC SVIVPMCTEK
MFZ4	IAMCQNLGYNVTKMPNLVGHELQTDALQLTTFTPLIQYGCSSQLQFFLC SVIVPMCTEK
HFZ5	VPMCRGIGYNLTHMPNQFNHDTQDEAGLEVHQFWPLVEIQ CSPDLRFFLCMTYPTICLPD
HFZ6	VPRCKMAYNMTFFPNLMGHYDQSI AAVEMEHFLPLANLECS PNIEFLCKAFVPTCI-E
MFZ6	VPRCKMTYNMTFFPNLMGHYDQSI AAVEMGHFLHLANLECS PNIEFLCQAFIPTCT-E
HFZ7	IPLCTDIAYNQTIMPNLLGHTNQEDAGLEVHQFYPLVKVQCSPELRFFLCSMYAPVCT-V
MFZ7	IPLCTDIAYNQTIMPNLLGHTNQEDAGLEVHQFYPLVKVQCSPELRFFLCSMYAPVCT-V
HFZ8	VPLCKGIGYNYTYMPNQFNHDTQDEAGLEVHQFWPLVEIQ CSPDLKFFLCSMYPTICLED
MFZ8	VPLCKGIGYNYTYMPNQFNHDTQDEAGLEVHQFWPLVEIQ CSPDLKFFLCSMYPTICLED
HFZ9	IPMCRGIGYNLTRMPNLLGHTSQGEAAAEALAEFAPLVQYGCCHSLRFFLC SLYAPMCTDQ
MFZ9	IPMCRGIGYNLTRMPNLLGHTSQGEAAAEALAEFSPLVQYGCCHSLRFFLC SLYAPMCTDQ
HFZ10	IPMCKDIGYNMTRMPNLMGHENQREAAIQLHEFAPLVEYGCCHGLRFFLC SLYAPMCTEQ

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FIG. 8B

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HFZ1	LEQALPPCRSLCERARQGCEALMNKFGFQWPDTLKCEKFPVHG--AGELCVGQNTSDKGT
MFZ1	LEQALPPCRSLCERARQGCEALMNKFGFQWPDTLKCEKFPVHG--AGELCVGQNTSDKGT
HFZ2	LEQAIPPCRSICERARQGCEALMNKFGFQWPERLRCEHFPRHG--AEQICVGQNHSDEGA
HFZ3	YGRVTLPCRRLCQRAYSECSKLMEMFGVPWPEDMECSRFPDCE-EPYPRLVDLNLG---
MFZ3	YGRVTLPCRRLCQRAYSECSKLMEMFGVPWPEDMECSRFPDCE-EPYPRLVDLNLVG---
HFZ4	INIPIGPCGGMCLSVKRRCEPVLKEFGFAWPESLNCSKFPQQN-DHNHMCMEGPGD----
MFZ4	INIPIGPCGGMCLSVKRRCEPVLREFGFAWPDTLNCSKFPQQN-DHNHMCMEGPGD----
HFZ5	YHKPLPPCRSVCERAKAGCSPLMRQYGFAPWPERMSCDRLPVLGRDAEVLCDYNRSEATT
HFZ6	QIHVVPPCRKLCEKVSDCKKLIDTFGIRWPEELECRLQYCD-ETVPVTFDPHTEF---
MFZ6	QIHVVLPCKRLCEKIVSDCKKLMDTFGIRWPEELECRLPHCD-DTVPVTSHPHTEL---
HFZ7	LDQAIPPCRSICERARQGCEALMNKFGFQWPERLRCEHFVHG--AGEICVGQNTSDGSG
MFZ7	LDQAIPPCRSICERARQGCEALMNKFGFQWPERLRCEHFVHG--AGEICVGQNTSDGSG
HFZ8	YKKPLPPCRSVCERAKAGCAPLMRQYGFAPWDRMRCDRLPEQG-NPDTLCMDYNRTDLTT
MFZ8	YKKPLPPCRSVCERAKAGCAPLMRQYGFAPWDRMRCDRLPEQG-NPDTLCMDYNRTDLTT
HFZ9	VSTPIACRPMCEQARLRCAPIEQFNFGWPDSDLCARLPTRN-DPHALCMEAPENA-TA
MFZ9	VSTPIACRPMCEQARLRCAPIEQFNFGWPDSDLCARLPTRN-DPHALCMEAPENA-TA
HFZ10	VSTPIACRVMCEQARLKCSPIMEQFNFKWPDSDLCKRLPNKN-DPNYLCMEAPNN----

. * : * * : : * : : .

HFZ1	PT---PSLLPEFWTSNPQHGGGGHRG-----
MFZ1	PT---PSLLPEFWTSNGQHGGGGYRG-----
HFZ2	-----PALLTTAPPPGLQPGAGGTPG-----
HFZ3	---EPTEGAPV-----A
MFZ3	---DPTEGAPV-----A
HFZ4	-----EE-----V
MFZ4	-----EE-----V
HFZ5	APPRPFPKPTLPG-----PPGA-----PASGG-----
HFZ6	---LGPQKKTE-----Q
MFZ6	---SGPQKKSD-----Q
HFZ7	GPGGGPTAYPTAPYLPDLPFTALPPG-----
MFZ7	GAGGSPTAYPTAPYLPDPPFTAMSP-----
HFZ8	AAPSPPRRLPPPPP-GEQPPSGSGHGRPPGARPPHRGGGRGGGGDAAAPPARGGGGGGK
MFZ8	AAPSPPRRLPPPPPGEQPPSGSGHSRPPGARPPHRGGSSRGSGDAAAPPARGG----K
HFZ9	GPAEPHKGLGMLPV-----A
MFZ9	GPTEPHKGLGMLPV-----A
HFZ10	GSDEPTRGSGLFPP-----L

FIG. 8C

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HFZ1 GFPGGAG----ASERGFSCPRALKVPSYLNHFLGEKDCGAPCEPTKVYGLMYFGPEEL
MFZ1 GYPGGAG----TVERGFSCPRALRVPSYLNHFLGEKDCGAPCEPTKVYGLMYFGPEEL
HFZ2 GPGGGGAPPRIATLEHPFHCPVLKVPSYLSYKFLGERDCAAPCEPARPDGSMFFSQEET
HFZ3 VQRDYG-----FWCPRELKIDPDLGYSFLHVRDCSPPCP----NMYFR--REEL
MFZ3 VQRDYG-----FWCPRELKIDPDLGYSFLHVRDCSPPCP----NMYFR--REEL
HFZ4 PLPHKTPI-----QPGEECHSVGTNSDQYIWKRLNCLVKCGYDAGLY--SRSAK
MFZ4 PLPHKTPI-----QPGEECHSVGSNSDQYIWKRLNCLVKCGYDAGLY--SRSAK
HFZ5 ECPAGGPFV-----CKCREPFVPIKESHPLYNKVRTGQVPCAVPCYOPSFSADER
HFZ6 VQRDIG-----FWCPRHLKTSGGQGYKFLGIDQCAPP CP----NMYFK--SDEL
MFZ6 VPRDIG-----FWCPKHLRTSGDQGYRFLGIEQCAPP CP----NMYFK--SDEL
HFZ7 ASDGRGRPAF-----PFSCPRQLKVPPYLGYRFLGERDCGAPCEPGRANGLMYFKEEER
MFZ7 -SDGRGRLSF-----PFSCPRQLKVPPYLGYRFLGERDCGAPCEPGRANGLMYFKEEER
HFZ8 ARPPGGGAAP---CEPGCQCRAPMVSVSERHPLYNRVKTGQIANCALPCHNPFFSQDER
MFZ8 ARPPGGGAAP---CEPGCQCRAPMVSVSERHPLYNRVKTGQIANCALPCHNPFFSQDER
HFZ9 PRPARPPG-----DLGPGAGSGTCENPEKFQYVEKSRSCAPRCGPGVEVFWSSRDK
MFZ9 PRPARPPG-----DSAPGPGSGGTCDNPEKFQYVEKSRSCAPRCGPGVEVFWSSRDK
HFZ10 FRPQRPHSAQ----EHPLKDGGPGRGGCDNPGKFHHVEKSASCAPLCTPGVDVYWSREDK

←
HFZ1 RFSRTWIGIWSVLCCASTLFTVLTYLVDMMRFSYPERPIIFLSGCTAVAVAYIAGFLL
MFZ1 RFSRTWIGIWSVLCCASTLFTVLTYLVDMPRFSYPERPIISLSGCTAVAVAYIAGFLL
HFZ2 RFARLWILTWSVLCCASTFTTTLTVDLMDRFRYPERPIIFLSGCTMVSVAIYAGFVLQ
HFZ3 SFARYFIGLISIICLSATLFTLTLIDVTRFRYPERPIIFYAVCYMMVSLIFFIGFLL
MFZ3 SFARYFIGLISIICLSATLFTLTLIDVTRFRYPERPIIFYAVCYMMVSLIFFIGFLL
HFZ4 EFTDIWMAVWASLCFISTFTVLTFLIDSSRFSYPERPIIFLSMCYNIYSIAYIVRLTVG
MFZ4 EFTDIWMAVWASLCFISTFTVLTFLIDSSRFSYPERPIIFLSMCYNIYSIAYIVRLTVG
HFZ5 TFATFWIGLWSVLCFISTSTTVATFLIDMDTFRYPERPIIFLSACYLCVSLGFLVRLVVG
HFZ6 EFAKSFIGTVSIFCLCATLFTLTLIDVRRFRYPERPIIYYSVCYSIVSLMYFIGFLLG
MFZ6 DFAKSFIGIVSIFCLCATLFTLTLIDVRRFRYPERPIIYYSVCYSIVSLMYFVGFLLG
HFZ7 RFARLWVGWWSVLCCASTLFTVLTYLFDMMRFSYPERPIIFLSGCTFMVAVAHVAGFLL
MFZ7 RFARLWVGWWSVLSASTLFTVLTYLVDMMRFSYPERPIIFLSGCTFMVAVAHVAGFLL
HFZ8 AFTVFWIGLWSVLCFVSTFATVSTFLIDMERFKYPERPIIFLSACYLFVSVGYLVRVAG
MFZ8 AFTVFWIGLWSVLCFVSTFATVSTFLIDMERFKYPERPIIFLSACYLFVSVGYLVRVAG
HFZ9 DFALVWMAVWSALCFSTFTVLTFLLEPHRFQYPERPIIFLSMCYNVYSLAFLIRAVAG
MFZ9 DFALVWMAVWSALCFSTFTVLTFLLEPHRFQYPERPIIFLSMCYNVYSLAFLIRAVAG
HFZ10 RFAVWLAIWAVLCFFSSAFTVLTFLIDPARFRYPERPIIFLSMCYCVYSGYLIRLFAG

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FIG. 8D

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→ extracellular domain loop 1

HFZ1	DRVVCNDK-----	FAEDGARTVAQGTTK
MFZ1	DRVVCNDK-----	FAEDGARTVAQGTNK
HFZ2	ERVVCNER-----	FSEDGYRTVVQGTKK
HFZ3	DRVACNAS-----	I---PAQYKASTVTQGSHN
MFZ3	DRVACNAS-----	S---PAQYKASTVTQGSHN
HFZ4	RERISCDF-----	EEAAEPVLIQEG LKN
MFZ4	RERISCDF-----	EEAAEPVLIQEG LKN
HFZ5	HASVACS-----	RE-----HNHIHYETTGP
HFZ6	DSTACNKA-----	D---EKLELGDTVVLGSON
MFZ6	NSTACNKA-----	D---EKLELGDTVVLGSKN
HFZ7	DRAVCVER-----	FSDDGYRTVAQGTKK
MFZ7	DRAVCVER-----	FSDDGYRTVAQGTKK
HFZ8	HEKVACSGGAPGAGGAGGAGGAAA-GAGAAGAGAGGPGGRGEYEELGAVEQHVR YETTGP	
MFZ8	HEKVACSGGAPGAGGRGGAGGAAAAGAGAAGRGASSPGARGEYEELGAVEQHVR YETTGP	
HFZ9	AQSVACD-----	QEAGALYVIOEGLEN
MFZ9	AQSVACD-----	QEAGALYVIOEGLEN
HFZ10	AESIACD-----	RDSGQLYVIOEGLES

←

HFZ1	EGCTILEMMLYFFSMASSIWWVILSLTWFLAAGMKWGHEAIEANSQYFHLAAWAVPAIKT
MFZ1	EGCTILEMMLYFFSMASSIWWVILSLTWFLAAGMKWGHEAIEANSQYFHLAAWAVPAIKT
HFZ2	EGCTILEMMLYFFSMASSIWWVILSLTWFLAAGMKWGHEAIEANSQYFHLAAWAVPAVKT
HFZ3	KACTMLEMILYFFTMAGSVWWVILTITWFLAAVPKWGSEAIEKKALLFHASAWGIPGTLT
MFZ3	KACTMLEMVL YFFTMAGSVWWVILTITWFLAAVPKWGSEAIEKKALLFHASAWGIPGTLT
HFZ4	TGCAIIFLLMYFFGMASSIWWVILTLTWFLAAGLKWGHEAIEMHSSYFHIAAWAIPAVKT
MFZ4	TGCAIIFLLMYFFGMASSIWWVILTLTWFLAAGLKWGHEAIEMHSSYFHIAAWAIPAVKT
HFZ5	ALCTIVFLLVYFFGMASSIWWVILSLTWFLAAMKWGNEAIEAGYQYFHLAAWLIPSVKS
HFZ6	KACTVLFMLLYFFTMAGTVWWVILTITWFLAAGRKWSCEAIEQKAVWFHAVAWGTPGFLT
MFZ6	KACSVFMFLYFFTMAGTVWWVILTITWFLAAGRKWSCEAIEQKAVWFHAVAWGAPGFLT
HFZ7	EGCTILEMVL YFFGMASSIWWVILSLTWFLAAGMKWGHEAIEANSQYFHLAAWAVPAVKT
MFZ7	EGCTILEMVL YFFGMASSIWWVILSLTWFLAAGMKWGHEAIEANSQYFHLAAWAVPAVKT
HFZ8	ALCTVVFLLVYFFGMASSIWWVILSLTWFLAAGMKWGNEAIEAGYSQYFHLAAWLIPSVKS
MFZ8	ALCTVVFLLVYFFGMASSIWWVILSLTWFLAAGMKWGNEAIEAGYSQYFHLAAWLIPSVKS
HFZ9	TGCTLVFLLLYFFGMASLWVVLTLTWFLAAGKKWGHEAIEAHGSYFHMAAWGLPALKT
MFZ9	TGCTLVFLLLYFFGMASLWVVLTLTWFLAAGKKWGHEAIEAHGSYFHMAAWGLPALKT
HFZ10	TGCTLVFLVL YFFGMASLWVVLTLTWFLAAGKKWGHEAIEANSYFHLAAWAI PAVKT

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FIG. 8E

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↪ extracellular domain loop 2 ◀

HFZ1	ITILALGQVDGDLVSGVCFVGLNNVDALRGFVLAPLFVYLFIGTSFLLAGFVSLFRIRTI
MFZ1	ITILALGQVDGDLVSGVCFGLNNVDALRGFVLAPLFVYLFIGTSFLLAGFVSLFRIRTI
HFZ2	ITILAMGQIDGDLVSGVCFVGLNSLDPLRGFVLAPLFVYLFIGTSFLLAGFVSLFRIRTI
HFZ3	IILLAMNKIEGDNISGVCFVGLYDVALRYFVLAPLCLYVVVGVSLLLAGIISLNRVRIE
MFZ3	IILLAMNKIEGDNISGVCFVGLYDVALRYFVLAPLCLYVVVGVSLLLAGIISLNRVRIE
HFZ4	IVILIMRLVDADELTGLCYVGNQNLDAITGFVAPLFTYLVIGTLFIAAGLVALEFKIRSN
MFZ4	IVILIMRLVDADELTGLCYVGNQNLDAITGFVAPLFTYLVIGTLFIAAGLVALEFKIRSN
HFZ5	ITALALSSVDGDPVAGICYVGNQNLNLRRLVGLPLVLYLLVGTFLLAGFVSLFRIRSV
HFZ6	VMLLAMNKVEGDNISGVCFVGLYDLASRYFVLLPLCLCVFVGLSLLLAGIISLNHVRQV
MFZ6	VMLLAMNKVEGDNISGVCFVGLYDLASRYFVLLPLCLCVFVGLSLLLAGIISLNHVRQV
HFZ7	ITILAMGQVDGDLVSGVCFVGLSSVDALRGFVLAPLFVYLFIGTSFLLAGFVSLFRIRTI
MFZ7	ITILAMGQVDGDLVSGVCFVGLSSVDALRGFVLAPLFVYLFIGTSFLLAGFVSLFRIRTI
HFZ8	IAVLALSSVDGDPVAGICYVGNQSLDNLRGFVLAPLVIYLFIGTMFLLAGFVSLFRIRSV
MFZ8	IAVLALSSVDGDPVAGICYVGNQSLDNLRGFVLAPLVIYLFIGTMFLLAGFVSLFRIRSV
HFZ9	IVILTLRKVAGDELTGLCYVASTDAAALTGFVLVPLSGYLVLGSSFLTGFVAFHIRKI
MFZ9	IVVLTLRKVAGDELTGLCYVASMDDPAALTGFVLVPLSCYLVLGTSFLTGFVAFHIRKI
HFZ10	ILILVMRRVAGDELTGVCYVGSMDVNALTGFVLIPLACYLVIGTSFILSGFVAFHIRRV
	: * : : . * : * : * : . ** : * : : * : : * : * : *

↪ extracellular domain loop 3

HFZ1	MKH--DGTKTEKLEKLMVRIGVFSVLYTVPATIVIACYFYEQAFRDQWERSWVAQSCKSY
MFZ1	MKH--DGTKTEKLEKLMVRIGVFSVLYTVPATIVIACYFYEQAFRDQWERSWVAQSCKSY
HFZ2	MKH--DGTKTEKLEKLMVRIGVFSVLYTVPATIVIACYFYEQAFREHWERSWVSQHCKSL
HFZ3	IPL--EKENQDKLVKFMIRIGVFSILYLVPLLVVIGCYFYEQAYRGIWETTQWIERCREY
MFZ3	IPL--EKENQDKLVKFMIRIGVFSILYLVPLLVVIGCYFYEQAYRGIWETTQWIERCREY
HFZ4	LQK--DGTKTDKLERLMVKIGVFSVLYTVPATCVIACYFYEQAFREHWERSWVSQHCKSL
MFZ4	LQK--DGTKTDKLERLMVKIGVFSVLYTVPATCVIACYFYEQAFREHWERSWVSQHCKSL
HFZ5	IKQ--GGTKTDKLEKLMIRIGIFTLLYTPASIVVACYLYEQHYRESWEAALTCACPGHD
HFZ6	IQH--DGRNQEKLLKFMIRIGVFSGLYLVPLVTLGCVVYEQVNRITWEITWVSDHCRQY
MFZ6	IQH--DGRNQEKLLKFMIRIGVFSGLYLVPLVTLGCVVYELVNRITWEMTWFSHCHQY
HFZ7	MKH--DGTKTEKLEKLMVRIGVFSVLYTVPATIVLACYFYEQAFREHWERTWLLQTCKSY
MFZ7	MKH--DGTKTEKLEKLMVRIGVFSVLYTVPATIVLACYFYEQAFREHWERTWLLQTCKSY
HFZ8	IKQQDGPTKTHKLEKLMIRGLFTVLYTPAAVVVACLFYEQHNRPRWEATHNCPCLRDL
MFZ8	IKQQGGPTKTHKLEKLMIRGLFTVLYTPAAVVVACLFYEQHNRPRWEATHNCPCLRDL
HFZ9	MKT--GGTNTKLEKLMVKIGVFSILYTPATCVIVCYVYERLNDWFRLRATEQPCTAA
MFZ9	MKT--GGTNTKLEKLMVKIGVFSILYTPATCVIVCYVYERLNDWFRLRATEQPCTAA
HFZ10	MKT--GGTNTKLEKLMVRIGLFSVLYTVPATCVIACYFXEHLNMDYWKILAAQHKCKM-
	: : . * : * : * : * : * * : : * . * : :

FIG. 8F

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HFZ1 AIPCPHLQAGGGAPPHPPMSPDFTVFMIKYLMTLIVGITS GFVIWSGKTLNSWRKFYTRL
MFZ1 AIPCPHLQGGGVPPHPPMSPDFTVFMIKYLMT-----LNSWRKFYTRL
HFZ2 AIPCP-----AHYTPR--MSPDFTVYMIKYLMTLIVGITS GFVIWSGKTLHSWRKFYTRL
HFZ3 HIPCP-----YQVTQMSRPDLILFLMKYLMALIVGIPSVFVWGSKKTCEWASFFHGR
MFZ3 HIPCP-----YQVTQMSRPDLILFLMKYLMALIVGIPSI FVWGSKKTCEWASFFHGR
HFZ4 -----EMLKIFMSLLVGITSGMWIWSAKTLHTWQ-KCSNR
MFZ4 -----EMLKIFMSLLVGITSGMWIWSAKTLHTWQ-KCSNR
HFZ5 TGQPR---AK-----PEYWVLM LKYFMCLVVGITSGVWIWSGKTVESWRRFTSRC
HFZ6 HIPCP-----YQAKAKARPELALFMIKYLMTLIVGISAVFVWGSKKTCTEWAGFFKRN
MFZ6 RIPCP-----YQANPKARPELALFMIKYLMTLIVGISAVFVWGSKKTCTEWAGFFKRN
HFZ7 AVPCP---PGHFPPM---SPDFTVFMIKYLMTMIVGITTGFVIWSGKTLQSWRRFYHRL
MFZ7 AVPCP---PRHFSPM---SPDFTVFMIKYLMTMIVGITTGFVIWSGKTLQSWRRFYHRL
HFZ8 QPDQA---RR-----PDYAVFMLKYFMCLVVGITSGVWVWSGKTLESWRS LCTRC
MFZ8 QPDQA---RR-----PDYAVFMLKYFMCLVVGITSGVWVWSGKTLESWRSALCTRC
HFZ9 AGPGG---RRDCSLPGGSVPTVAVFMLKIFMSLVVGITSGVWVWSKTFQTWQSLCYRK
MFZ9 TVPGG---RRDCSLPGGSVPTVAVFMLKIFMSLVVGITSGVWVWSKTFQTWQSLCYRK
HFZ10 NNQTK---TLDC-LMAASIPAVEIFMVKIFMLLVVGITSGMWIWSKTLQSWQVCSRR

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HFZ1 TN--SKQGETTV-----
MFZ1 TN--SKQGETTV-----
HFZ2 TN--SRHGETTV-----
HFZ3 RKKEIVNESRQVLQEP-----DFAQSLLRDPNTPIIRKSRGTSTQGTSTHAS
MFZ3 RKKEIVNESRQVLQEP-----DFAQSLLRDPNTPIIRKSRGTSTQGTSTHAS
HFZ4 LVNSGKVKREKRGNGW-----VKPGKGSE-----
MFZ4 LVNSGKVKREKRGNGW-----VKPGKGNE-----
HFZ5 CC-RPRRGHKSGGA-----MA--AG-D-----
HFZ6 RKRDPISER RVLQESCEFFLKHNSKVKKKKHYKPSSHKLKVISKSMGTSTGATANHGT
MFZ6 RKRDPISER RVLQESCEFFLKHNSKVKKKKHGAPGPHRLKVISKSMGTSTGATTNHGT
HFZ7 SH--SSKGETAV-----
MFZ7 SH--SSKGETAV-----
HFZ8 CW-ASKGA AVGGGAGA-----TAAGGGGGPGGGGGGP
MFZ8 CW-ASKGA AVGAGAGG-----SGPGGSGP-----GP
HFZ9 IA--AGRARAKACRAP-----GSYGRGTHC-----
MFZ9 MA--AGRARAKACRTP-----GGYGRGTHC-----
HFZ10 LKKKSRRKPASVITSG-----GIYKKAQH-----

FIG. 8G

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HFZ1	-----
MFZ1	-----
HFZ2	-----
HFZ3	STQLAMVDDQRSKAGSIHKSIVSSYHGSLHRSRDGRYTPCSYRG--MEERLPHGMS-RLT
MFZ3	STQLAMVDDQRSKAGSVHKSIVSSYHGSLHRSRDGRYTPCSYRG--MEERLPHGMS-RLT
HFZ4	-----TVV-----
MFZ4	-----TVV-----
HFZ5	-----YPEASAALTGRGTGPPGPAATYHKQVSLSHV-----
HFZ6	SAVAITSHDYLGOETLLEIQTSPETSMREVKADGASTPRLREQDCGEPASPAASIS-RLS
MFZ6	SAMAIADHDYLGQETSTEVTSPESVKEGRADRANTPSAKDRDCGESAGPSSKLSGNRN
HFZ7	-----
MFZ7	-----
HFZ8	GGGGGPGGGGSLYSDVSTGLTWRSGTAS-SVSYPKQMPLSQV-----
MFZ8	GGGGGPGGGGSLYSDVSTGLTWRSGTAS-SVSYPKQMPLSQV-----
HFZ9	-----H---YKAPTIVLHMTKTDPSLENPTL-----
MFZ9	-----H---YKAPTIVLHMTKTDPSLENPTL-----
HFZ10	-----PQKT-HHGKYEIPAQSPTCV-----

HFZ1	-----
MFZ1	-----
HFZ2	-----
HFZ3	DHSRHSSSHRLNEQSRHSSIRDLSNNPMTHITHGTSMNRVIEEDGTS-----
MFZ3	DHSRHSSSHRLNEQSRHSSIRDLSNNPMTHITHGTSMNRVIEEDGTS-----
HFZ4	-----
MFZ4	-----
HFZ5	-----
HFZ6	GEQVDGKG--QAGSVSESARSEGRISPKSDITDTGLAQSNLQVPSSSEPSSLKGSTSL
MFZ6	GRESRAGGLKERSNGSEGAPSEGRVSPKSSVPETGLIDCSTSQAASSPEPTSLKGSTSLP
HFZ7	-----
MFZ7	-----
HFZ8	-----
MFZ8	-----
HFZ9	-----
MFZ9	-----
HFZ10	-----

FIG. 8H

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HFZ1	-----
MFZ1	-----
HFZ2	-----
HFZ3	-----
MFZ3	-----
HFZ4	-----
MFZ4	-----
HFZ5	-----
HFZ6	VHPVSGVRKEQGGGCHSDT
MFZ6	VHSASRARKEQGAGSHSDA
HFZ7	-----
MFZ7	-----
HFZ8	-----
MFZ8	-----
HFZ9	-----

FIG. 8I